



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/70	A1	(11) International Publication Number: WO 00/35461 (43) International Publication Date: 22 June 2000 (22.06.00)
(21) International Application Number: PCT/US99/30234 (22) International Filing Date: 17 December 1999 (17.12.99) (30) Priority Data: 60/112,984 17 December 1998 (17.12.98) US (71) Applicant (for all designated States except US): PATHOGEN-ESIS CORPORATION [US/US]; 201 Elliott Avenue West, Seattle, WA 98119 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MONTGOMERY, Alan, B. [US/US]; 3455 Evergreen Point Road, Medina, WA 98039 (US). BAKER, William, R. [US/US]; 4759 171st Street S.E., Bellevue, WA 98006 (US). (74) Agent: SHELTON, Dennis, K.; Christensen O'Connor Johnson & Kindness PLLC, Suite 2800, 1420 Fifth Avenue, Seattle, WA 98101 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHOD FOR THE TREATMENT OF SEVERE CHRONIC BRONCHITIS (BRONCHIECTASIS) WITH AN AEROSOLIZED ANTIBIOTIC (57) Abstract <p>A method for treatment of severe chronic bronchitis (bronchiectasis) using a concentrated aminoglycoside antibiotic formulation delivering the antibiotic to the lung endobronchial space including alveoli in an aerosol or dry powder having mass medium diameter predominately between 1 to 5 microns. The method comprises administration of the antibiotic in a concentration one to ten thousand times higher than the minimal inhibitory concentration of the target organism. Preferably, the method comprises endobronchial administration of aerosol or dry powder tobramycin to treat pseudomonal infections in severe chronic bronchitis (bronchiectasis) patients.</p>		

**METHOD FOR THE TREATMENT OF SEVERE CHRONIC BRONCHITIS
(BRONCHIECTASIS) WITH AN AEROSOLIZED ANTIBIOTIC**

Field of the Invention

The invention relates to methods and compositions for the treatment of severe
5 chronic bronchitis or bronchiectasis by endobronchial delivery of aminoglycoside
antibiotic compounds, such as tobramycin. In particular, the invention concerns
formulations including aminoglycoside powders or concentrated solutions having pH
between 5.5 and 7.0. The formulations permit delivery of aminoglycoside antibiotic
10 compounds to the lung endobronchial space of airways in dry powder form or as an
aerosol having mass medium average diameter predominantly between 1 to 5 μ . The
formulated and delivered efficacious amount of aminoglycoside antibiotic compound,
such as tobramycin, is sufficient for treatment and prophylaxis of acute and chronic
endobronchial infections, particularly those caused by the bacterium *Pseudomonas*
aeruginosa. In other aspects, the invention relates to the endobronchial delivery of
15 effective amounts of an aminoglycoside antibiotic, such as tobramycin, to patients with
bronchiectasis with *P. aeruginosa* to cause substantially complete eradication of the
organism. The novel formulations have small volume yet deliver effective doses of
aminoglycoside antibiotic compounds to the site of the infection.

Background of the Invention

20 Bronchiectasis is defined as irreversible abnormal dilatation of the airways.
Bronchiectasis can be caused by either acquired or congenital mechanisms that disrupt

order to achieve high sputum concentrations (Pennington J.E., "Penetration of antibiotics into respiratory secretions," *Rev Infect Dis* 3(1):67-73 (1981)). High doses and multiple courses of therapy lead to high serum concentrations and increase the risk of serious adverse effects, such as ototoxicity and nephrotoxicity. Treatment of patients with bronchiectasis with *P. aeruginosa* seldom, if ever, eradicates the organisms – most of the treatment benefit from either oral or IV antibiotics just suppresses growth, with regrowth occurring after discontinuation of antibiotic therapy. Therefore, any method that can eradicate infection for any period of time would be useful, novel and an advance in the art.

Tobramycin is commonly prescribed for the treatment of serious infections with *P. aeruginosa*. It is an aminoglycoside antibiotic produced by the actinomycete, *Streptomyces tenebrarius*. Low concentrations of tobramycin ($< 4 \mu\text{g/mL}$) are effective in inhibiting the growth of many Gram-negative bacteria and under certain conditions may be bactericidal (Neu, H.C., "Tobramycin: an overview," *J Infect Dis* 134, Suppl: S3-19 (1976)). Tobramycin is poorly absorbed across mucosal surfaces, necessitating parenteral administration. Tobramycin activity is inhibited by purulent sputum: high concentrations of divalent cations, acidic conditions, increased ionic strength and macromolecules that bind the drug all inhibit tobramycin in this environment. It is estimated that 5-10X higher concentrations of tobramycin are required in the sputum to overcome these inhibitory effects (Levy J. et al., "Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serum," *J Infect Dis* 148(6):1069-76 (1983)).

Delivery of the poorly absorbed antibiotic tobramycin to the airway by the aerosol route of cystic fibrosis (CF) patients has been documented using the aerosol route. Much of this work has been done toward treatment of chronic lung infections with *P. aeruginosa* in cystic fibrosis (CF) patients. A multicenter, double blind, placebo-controlled, crossover trial of 600 mg tid of aerosolized tobramycin for endobronchial infections due to *P. aeruginosa* in 71 CF patients demonstrated a significant reduction in sputum density of this pathogen as well as improved spirometry in the treatment group. Emergence of *P. aeruginosa* strains highly resistant to tobramycin (defined as $\text{MIC} \geq 128 \mu\text{g/mL}$) was comparable in the placebo and treatment groups. The presence

jet nebulizer. The particle size is identical. The one-way valves also decrease the potential for accidental spillage and allow for the use of an expiratory filter. For these reasons, the Pari® LC Plus jet nebulizer was selected for use in two large Phase 3 trials of TOBI for chronic *P. aeruginosa* infection in CF patients. Preliminary data from these Phase 3 studies show that mean peak sputum tobramycin concentrations achieved using the Pari LC Plus jet nebulizer are significantly higher than those using the Pari® LC jet nebulizer as described in Eisenberg et al. (1997), *supra*.

Two placebo-controlled, multicenter, randomized, double-blind clinical trials of intermittent administration of inhaled tobramycin in cystic fibrosis patients with *Pseudomonas aeruginosa* infection were reported in Ramsey, B.W. et al., "Intermittent Administration of Inhaled Tobramycin in Patients with Cystic Fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group." N. Engl. J. Med. 340(1):23-30 (1999). In these studies, five hundred twenty subjects were randomized to receive either 300 mg inhaled tobramycin or placebo twice daily for 28 days followed by 28 days off study drug. Subjects continued on treatment or placebo for three "on-off" cycles for a total of 24 weeks. Efficacy variables included sputum *P. aeruginosa* density. Tobramycin-treated patients had an average 0.8 log₁₀ decrease in *P. aeruginosa* density from Week 0 to Week 20, compared with a 0.3 log₁₀ increase in placebo-treated patients (P<0.001). Tobramycin-treated patients had an average 1.9 log₁₀ decrease in *P. aeruginosa* density from Week 0 to Week 4, compared with no change in placebo-treated patients (P<0.001).

Summary of the Invention

One aspect of the current invention is a method for treatment of severe chronic bronchitis or bronchiectasis caused by *Pseudomonas aureginosa* or other pseudomonads by administering to the patient requiring such treatment a formulation comprising about one to ten thousand times higher concentration of an effective aminoglycoside antibiotic, such as tobramycin, than its minimal inhibitory concentration (MIC).

In another aspect, the current invention provides methods for treatment of severe chronic bronchitis or bronchiectasis caused by *Pseudomonas aureginosa* or other pseudomonads by administering to a patient requiring such treatment effective amounts of a suitable aminoglycoside antibiotic by an endobronchial route of administration. In a representative embodiment of this aspect of the invention, the antibiotic may be

safety of inhaled tobramycin for treatment of patients with bronchiectasis and *P. aeruginosa*. The results obtained in bronchiectasis were highly significant, with the antimicrobial efficacy greater than 10,000 fold greater than in cystic fibrosis patients. In the study, 20% of the bronchiectasis patients had complete eradication, a finding rare with either oral or intravenous therapy. In fact, in spite of 20 years of use of intravenous tobramycin, usually in combination with another antibiotic, results such as these have not been reported. Thus, the results obtained teach the following:

1. Aerosolized aminoglycoside antibiotics can be extremely effective in treatment of bronchiectasis;
2. The aerosol route improves the efficacy of an agent even if given intravenously; and
3. The duration of therapy does not need to be long term; efficacy was seen in two weeks.

Since bronchiectasis is the most severe form of chronic bronchitis, these results teach that short course aerosol antibiotics are effective in treating the disorder.

Brief Description of the Drawings

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same becomes better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 depicts subdivisions and structure of intrapulmonary airways.

FIGURE 2 is an outline of the study described in Example 1.

FIGURE 3 is a graphical representation of the mean change in sputum *P. aeruginosa* density, as described in Example 1. Patients received TSI or placebo twice daily between Weeks 0 and 4. At baseline, n = 37 for both groups. The error bars shown in FIGURE 3 represent 95% confidence intervals.

FIGURE 4 depicts a jet nebulizer suitable for aerosolization of an concentrated antibiotic solution of the invention.

Detailed Description of the Preferred Embodiment

As used herein:

"Normal saline" means water solution containing 0.9% NaCl.

NaCl. Quarter normal saline, that is 0.225% of sodium chloride, is a presently preferred vehicle for delivery of aminoglycoside into endobronchial space.

By way of illustration, high concentrations of tobramycin administered to the lungs by aerosolization result in maximization of sputum levels of tobramycin and in minimization of tobramycin serum levels. Thus, administration of tobramycin by aerosolization has the advantage of reducing systemic toxicity while providing efficacious concentrations of tobramycin in the sputum. The bronchial barrier restricts the movement of aerosolized tobramycin and prevents it from reaching high systemic levels.

Aerosolized formulation of tobramycin delivers high concentrations of the drug directly to the airways with low systemic absorption. Aerosolized formulations of concentrated tobramycin are preferably nebulized by a jet, ultrasonic or electronic nebulizer capable of producing tobramycin aerosol having a particle size predominately between 1 and 5 microns. Particles of these sizes are preferred for efficacious delivery of concentrated tobramycin into the endobronchial space in order to treat chronic bronchitis infections. To achieve high concentrations of tobramycin solution in both the upper and lower airways and in sputum, tobramycin is preferentially nebulized in jet nebulizers, particularly those modified with the addition of one-way flow valves, such as for example, Pari LC Plus TM nebulizer, commercially available from Pari Respiratory Equipment, Inc., Richmond, Virginia, which delivers up to 20% more drug than the other unmodified nebulizers.

The tobramycin aerosol formulation contains a high concentration from about 4 to about 100 mg/ml, more preferably about 8 to about 80 mg/ml, and most preferably about 60 mg/mL of tobramycin sufficient for *Pseudomonas aeruginosa* suppression or eradication, formulated in the smallest possible volume of about 1-5 mL of a physiologically acceptable solution, preferably in one quarter strength of normal saline, having a salinity adjusted to permit generation of tobramycin aerosol well-tolerated by patients but to prevent the development of secondary undesirable side effects such as bronchospasm and cough.

In other aspects, the aminoglycoside antibiotic compounds of the invention may be endobronchially administered in a dry powder formulation for efficacious delivery of the finely milled antibiotic into the endobronchial space using dry powder or metered

collection efficiencies (50 to 80% recovery is typical). Both techniques and any and all improvements thereof are intended to be within the scope of the invention.

In other embodiments, the dry powder formulations may be prepared by spray drying or solution precipitation techniques. Spray drying is achieved by spraying a fine mist of drug solution onto a support and drying the particles. The particles are then collected. Spray drying has the advantage of being the least prone to degrading chemical entities. Solution precipitation is performed by adding a co-solvent that decreases the solubility of a drug to a uniform drug solution. When sufficient co-solvent is added, the solubility of the drug falls to the point where solid drug particles are formed which can be collected by filtration or centrifugation. Precipitation has the advantage of being highly reproducible and can be performed under low temperature conditions which reduce degradation.

The dry powder formulations of the invention may be used directly in metered dose or dry powder inhalers. A metered dose inhaler consists of three components: a canister containing the propellant/drug suspension, a metering valve designed to deliver accurately metered volumes of the propellant suspension, and an oral adapter which contains a spray orifice from which the metered dose is delivered. In the rest position, the metering chamber of the valve is connected to the drug suspension reservoir via a filling groove or orifice. On depression of the valve this filling groove is sealed and the metering chamber is exposed to atmospheric pressure via the spray orifice in the oral adapter and the valve stem orifice. This rapid pressure reduction leads to flash boiling of the propellant and expulsion of the rapidly expanding mixture from the metering chamber. The liquid/vapor mixture then enters the expansion chamber, which is constituted by the internal volume of the valve stem and the oral adapter. The mixture undergoes further expansion before being expelled, under its own pressure, from the spray nozzle. On exit from the spray orifice, the liquid ligaments which are imbedded in propellant vapor are torn apart by aerodynamic forces. Typically, at this stage the droplets are 20 to 30 microns in diameter and are moving at the velocity of sound of the two-phase vapor liquid mixture (approximately 30 meters/second). As the cloud of droplets moves away from the spray nozzle, it entrains air from the surroundings and decelerates, while the propellant evaporates through evaporation, the entrained droplets eventually reach their residual diameter. At this point, the particles/droplets consist of a

fourteen days. The dry powder formulations are temperature stable and have a physiologically acceptable pH of 4.0-7.5, preferably 6.5 to 7.0, and long shelf lives.

The tobramycin aerosol formulation of the invention contains at least one thousand but usually about ten thousand times higher concentration of tobramycin than is its minimum inhibitory amount. Tobramycin is nebulized predominantly into particle sizes which are delivered to the terminal and respiratory bronchioles and alveoli (lower lungs) where the respiratory pathogens are present. Moreover, high concentration of aerosolized tobramycin comes into contact with the sputum, penetrates it and kills bacteria present there.

Subdivision and structure of intrapulmonary airways (lower lung) are seen in FIG. 1. Respiratory microbial pathogens are present in the upper airways, in bronchi and bronchioli, particularly in terminal and respiratory bronchioles. During exacerbation of infection, bacteria can also be found to be present in alveoli. Any therapeutic formulation must be, therefore, delivered to the terminal bronchioles and to alveoli.

The foregoing and other aspects of the invention may be better understood in connection with the following representative examples.

Example 1 In Vivo Clinical Study

A placebo-controlled, double-blind, randomized study was conducted to evaluate the microbiological efficacy and safety of inhaled tobramycin for treatment of patients with bronchiectasis and *P. aeruginosa*. Patients with *P. aeruginosa* ($\geq 10^4$ colony forming units/g sputum) were randomly assigned to receive either Tobramycin Solution for Inhalation (TSI) (n=37) or placebo (n=37) twice daily for 4 weeks. The change in *P. aeruginosa* density in sputum was measured at Weeks 2, 4, and 6 (2 weeks post-treatment). Clinicians assessed patients' general medical condition at Week 6. Safety parameters included adverse events, serum chemistry, and airway reactivity. At Week 4, the TSI group had a mean decrease in *P. aeruginosa* of 4.54 log₁₀ colony forming units/g sputum compared with no change in the placebo group (p<0.001). At Week 6, *P. aeruginosa* was eradicated in 35% of TSI-treated patients but was detected in all placebo patients. Investigators indicated 62% of TSI patients versus 38% of placebo patients showed an improved medical condition (odds ratio=2.7, 95% CI: 1.1-6.9). More

Week 0, prior to and 30 minutes after the patient administered study drug, the forced expiratory volume at one second (FEV₁) was measured by standard American Thoracic Society methodology to monitor airway reactivity (American Thoracic Society. Standardization of spirometry. Amer J Respir Crit Care Med 1995;152:1107-36). Blood was drawn 30-60 minutes after drug administration for analysis of serum tobramycin concentration. At Week 4, airway reactivity was again monitored, a medical exam was performed, and laboratory tests that were performed at screening were repeated.

Serum chemistry, hematology, and serum tobramycin concentrations were performed at a central laboratory. Quantitative sputum bacterial culture and measurement of tobramycin minimum inhibitory concentrations (MIC) for *P. aeruginosa* were performed at a central laboratory (Children's Hospital and Regional Medical Center, Seattle, WA) as described by Burns et al., "Microbiology of sputum from patients at cystic fibrosis centers in the United States," *Clin Infect Dis* 27:158-63 (1998). Sputum samples collected at each study visit were shipped on wet ice for receipt within 48 hours at the central laboratory.

Endpoints

The primary efficacy endpoint was the change in *P. aeruginosa* density (expressed as log₁₀ CFU/g sputum) from baseline to Week 4. Additional efficacy endpoints included the following: (1) the change in *P. aeruginosa* density from baseline to Week 2 and to Week 6; (2) an investigator's assessment of change in the patient's general medical condition ("improved" or "not improved") throughout the study (recorded at Week 6); (3) the percent change in FEV₁ % predicted and in forced vital capacity (FVC) % predicted from Week 0 to Week 4. Percent predicted values were calculated by dividing the actual values of FEV₁ or FVC by the values predicted by the Knudson equations for normal, healthy individuals based on gender, age, and height and multiplying by 100.²⁰ Safety endpoints included the incidence of adverse events, change in serum chemistry and hematology measurements, and airway reactivity.

Each patient's microbiological response was categorized according to whether *P. aeruginosa* was eradicated, reduced by treatment, or did not respond to treatment. *P. aeruginosa* was considered eradicated if it was not detected at Week 6 or if the patient was unable to produce a sputum sample at Week 6 and *P. aeruginosa* was not isolated at Week 4. A patient's response was defined as reduced by treatment if *P. aeruginosa* was

age, race, *P. aeruginosa* density in sputum, and pulmonary function. Both treatment groups adhered to the dosing requirements; 81% of patients in the TSI group and 86% in the placebo group used more than 80% of the drug doses.

Table 1
Demographics and Baseline Characteristics

Characteristic	TSI (n = 37)	Placebo (n = 37)	p-value
Gender			
Female*	23 (62.2%)	22 (59.5%)	1.000 [‡]
Age in years [†]	66.6 (13.0)	63.2 (13.5)	0.270 [§]
Race			
Caucasian*	36 (97.3%)	32 (86.5%)	0.199 [‡]
<i>P. aeruginosa</i> log ₁₀ CFU/g sputum [†]	7.1 (1.4)	6.7 (1.6)	0.331 [§]
FEV ₁ % predicted [†]	56.2 (21.2)	53.3 (22.1)	0.574 [§]
Duration of bronchiectasis in years [†]	14.1 (15.4)	18.7 (17.0)	0.232 [§]
History of smoking*	24 (64.9%)	16 (43.2%)	0.102 [‡]

n (%)

[†] Mean (SD)

[‡] Treatment groups were compared using Fisher's Exact test.

[§] Treatment groups were compared using two-sample, two-sided t tests.

As shown in FIG. 3, at all time points of the study, patients treated with TSI had a significant reduction in sputum *P. aeruginosa* compared with patients treated with placebo. At the end of treatment (Week 4), TSI-treated patients had a mean decrease of 4.54 log₁₀ CFU/g sputum compared with a mean increase of 0.02 log₁₀ CFU/g sputum in patients receiving placebo ($p < 0.001$). After the two-week follow-up period (Week 6), the mean reduction observed in the TSI group was smaller than at previous weeks, indicating that some re-growth of the organism had occurred following the cessation of TSI therapy. The placebo group showed negligible change in *P. aeruginosa* density at all time points.

At the end of the study (Week 6), more TSI-treated patients (23 of 37, 62%) than placebo-treated patients (14 of 37, 38%) were assessed as having an improved medical condition. The odds that a patient receiving TSI would improve were 2.7 times higher than for a patient who received placebo (95% CI: 1.1 – 6.9). In addition to treatment group, gender was also a significant predictor of clinical improvement; 62% of women were assessed as improved compared with 31% of men ($p = 0.010$). Other baseline

Table 2
Incidence of Treatment-Emergent Adverse Events
Occurring in Greater than 10% of TSI Patients

Symptom	TSI (n = 37)	Placebo (n = 37)
Patients reporting 1 adverse event*	31 (83.8%)	31 (83.8%)
Increased cough	15 (40.5%)	9 (24.3%)
Dyspnea	12 (32.4%)	3 (8.1%)
Increased sputum	8 (21.6%)	5 (13.5%)
Chest pain	7 (18.9%)	0
Wheezing	6 (16.2%)	0
Fatigue	5 (13.5%)	6 (16.2%)
Hemoptysis [†]	5 (13.5%)	3 (8.1%)
Fever	4 (10.8%)	6 (16.2%)
Decreased sputum production	5 (13.5%)	0

n (%)

- 5 † Mild or moderate, including blood-streaked sputum; no severe hemoptysis occurred in either group.

Events reported as chest pain appeared to be related to the respiratory system based on investigator comments (e.g., chest tightness and pleuritic pain) and on the treatment interventions (bronchodilators and analgesics). Physicians commented that the adverse events were related to study drug for 12 of 15 TSI-treated patients reporting increased cough, for 3 of 12 patients experiencing dyspnea, for 3 of the 6 patients with wheezing, and for 3 of the 7 patients reporting chest pain.

Patients hospitalized and treated for exacerbation of their pulmonary disease included 4 patients in the TSI group and one patient in the placebo group. The placebo patient and 3 of the 4 TSI-treated patients were treated with intravenous antibiotics. The fourth TSI patient received anti-inflammatory drugs but continued to administer TSI while in the hospital. The patient completed the study and *P. aeruginosa* was eradicated from her sputum. Another TSI-treated patient who withdrew from the study experienced an increase in respiratory symptoms and was hospitalized for treatment several days after withdrawal.

Acute airway reactivity, defined for this study as a decrease of greater than 12% in FEV₁ 30 minutes after drug administration, occurred in 3 of 36 (8.3%) TSI patients and in 6 of 37 (16.2%) placebo patients. All of the TSI-treated patients and 4 of 6

(8 l/M) is connected to nebulizer's liquid medicine cup 22. Air goes through the cup 22 into jet nebulizer orifice 26 where it creates aerosol by shearing the liquid solution into small threads of liquid that shatter into small particles when it hits a baffle 18. The nebulizer 10 further comprises a mouthpiece 30 for inhalation of aerosol. The mouthpiece contains flapper valve 12 to allow exhalation. The mouthpiece 30 is connected to the main body of the nebulizer 10.

To identify efficient and suitable nebulizer for use in the current invention, two separate studies were performed.

The first study, described below, was to determine in vitro which nebulizers meet criteria that are important for delivery of aerosolized antibiotics. Both ultrasonic and jet nebulizers were studied. The second study was to determine the pharmacodynamics of tobramycin in the sputum which is a measure of the efficacy of the aerosol delivery.

The major limitation of the Ultraneb® 99 (DeVilbiss) ultrasonic nebulizer used for delivery of tobramycin formulation are its high-cost, waste of the drug and inconvenience. As seen from Table 3, this nebulizer requires 30 ml of the drug solution, and it has large, 1200 ml aerosol reservoir. In order for tobramycin aerosol therapy to be widely available and used by patients with chronic bronchitis in ambulatory or home setting, a more efficient and easier to use nebulizer is needed.

This study was the first step in testing whether the first jet nebulizer could be substituted for ultrasonic nebulizer and whether adequate sputum aminoglycoside levels can be obtained with a jet nebulizer. Subsequent studies included long-term clinical efficacy.

An in vitro comparative study evaluated a variety of commercially available jet nebulizers, including among others, the Acorn II® by Marquest, T-Updraft® by Hudson, Sidestream® by Medicaid, and Pari LC® by Pari. The PulmoAide® compressor was designed.

A closer look at all these nebulizers revealed that most of them are relatively inefficient in delivering an inhalable mist. The three chosen nebulizers used in the clinical protocols, the ultrasonic DeVilbiss 99, the Pari LC jet and the Medicaid Sidestream jet, have shown properties suggesting that they could possibly deliver tobramycin aerosol into endobronchial space. Of the three, two jet nebulizers were clearly superior to the ultrasonic DeVilbiss. Therefore, they have been evaluated in vitro

particle size output. Conversely, the Pari LC produces a larger particle size (4.5μ) at a higher output thus reducing the delivery time and patient's discomfort. Both jet nebulizers have a Venturi design which increases drug delivery within inspiration. The smaller equipment size decreases the fallout of aerosolized particles that occurs prior to inspiration by the patient. The jet nebulizers Sidestream and Pari LC also have the advantage of being available in both reusable disposable units.

As also seen in Table 3, all three nebulizers delivered about 30 mg/ml of tobramycin to the airways even though the ultrasonic DeVilbiss 99 nebulizer needed twice as much drug, that is 600 mg of tobramycin compared with 300 mg for the two jet nebulizers, for delivery of 33 mg/ml.

The current invention tested and identified two jet nebulizers which are able to deliver the tobramycin efficacy equivalence by using only one-half of the dosage needed by ultrasonic nebulizer.

In addition to the above tested jet nebulizers, two small volume ultrasonic nebulizers, Aerosonic by DeVilbiss and UltraAire by Omron were also tested and found suitable for delivery of the formulation of the invention. These ultrasonic nebulizers differ from the UltraNebb 99 ultrasonic as they have a smaller reservoir and can use the smaller volume solution.

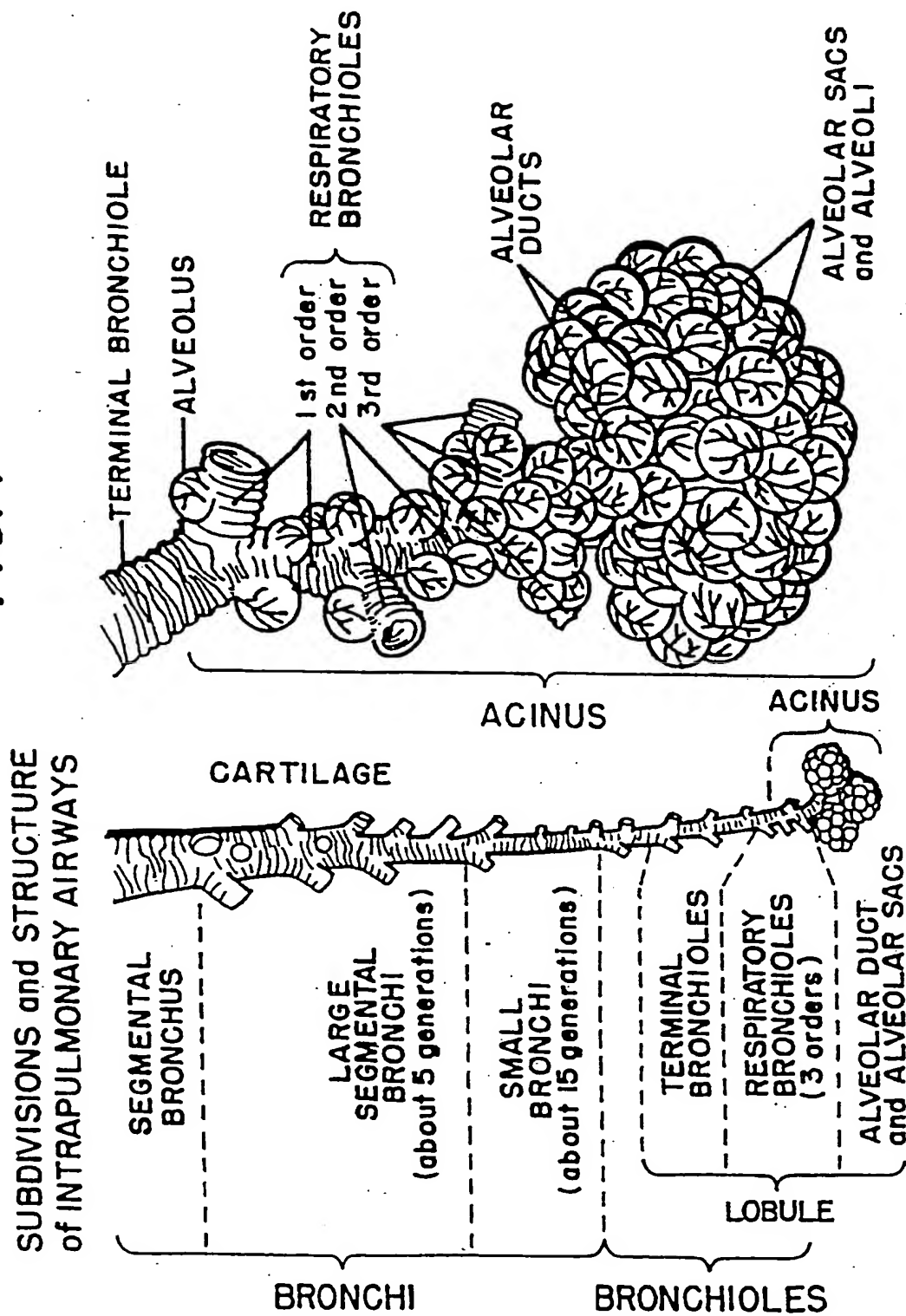
UTILITY

The utility of this invention is that this small volume, high concentration formulation of an aminoglycoside, such as tobramycin, can be used by either a jet or hand-held ultrasonic nebulizer and deliver efficacious concentrations of the drug to the endobronchial space in people with severe chronic bronchitis (bronchiectasis) due to aminoglycoside susceptible bacteria or other infections. The formulation is safe and very cost effective. Furthermore, the formulation is kept in a nitrogen environment and with pH controlled to provide adequate shelf life for commercial distribution.

While the preferred embodiments of the invention have been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

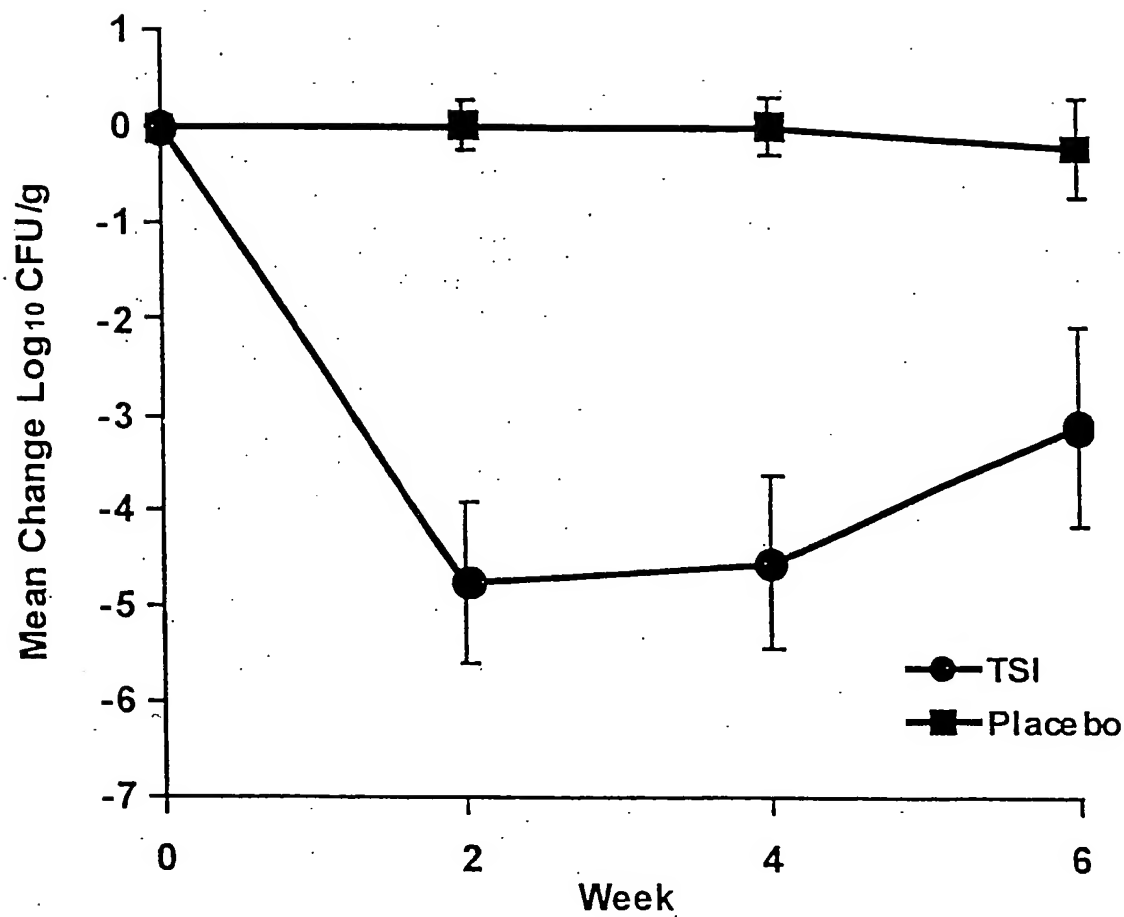
9. The method in Claim 2 wherein the amino glycoside antibiotic is tobramycin.
10. The method in Claim 1 wherein the antibiotic is administered in an aerosol or in a dry powder form.
11. The method in Claim 10 wherein the antibiotic is administered in an aerosol form.
12. The method of Claim 11 wherein the aerosol is delivered by a jet, ultrasonic or electronic nebulizer.
13. The method in Claim 11 wherein the antibiotic is administered in a formulation that upon aerosolization has particle sizes between about 1 and 5 microns.
14. The method in Claim 10 wherein the antibiotic is administered in a dry powder form.
15. The method of Claim 14 wherein the dry powder is delivered by a dry powder inhaler or by a metered dose inhaler.
16. The method in Claim 12 wherein the dry powder has particle sizes between about 1 and 5 microns.
17. The method in Claim 10 wherein the antibiotic is administered in a formulation have a pH between about 5.5 and 6.5.
18. A method of Claim 1 wherein from about 1 to 400 mg of the antibiotic is administered twice daily for at least five days.

FIG. 1



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**FIG 3**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/30234

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/70

US CL :514/34, 37, 39, 41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/34, 37, 39, 41

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,522,385 A (LLOYD et al.) 04 June 1996.	1-22
A	US 5,512,269 A (VEDIA et al.) 30 April 1996.	1-22
A	US 5,141,674 A (LEIGH) 25 August 1992.	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

RAYMOND J. HENLEY III

Telephone No. (703) 308-1235